

the slime inside us

Vivienne Baillie Gerritsen

When I was small, I used to visit an elderly lady who lived next door to us. With her, I would make rice-filled frogs. The kind you can fling from one end of a room to land flat, with a plod and no bounce, onto the arm of a chair or the back of a sofa. In the 1970s, these colourful frogs haunted every household in the UK. As I painstakingly cut out frog-shaped pieces of paisley-patterned material, Lady Clarke, as she was called, used to tower over me, observing my every move with a drop always hanging off the end of her nose. I would sit there terrified that it would lose grip and drip on to me. But it never did. It just wobbled, menacingly, until it was wiped away with a handkerchief Lady Clarke kept tucked up one of her sleeves. That drop was mucus. Besides exuding from our nose, especially when we have a cold or when we get old, mucus lines the mucous membranes of our body, where it keeps things lubricated and, generally, healthy. Mucus is composed of a lot of water and several macromolecules, among them glycoproteins that carry sialic acid. Why sialic acid? Because it helps to keep pathogens away. And how does it get there? By way of sialyltransferases.



etched linoprint by Emily Harvey
www.thequiriousprintmaker.co.uk

courtesy of the artist

Mucus is a protective lining for the epithelium and a very effective lubricant that keeps epithelial cells bathed in a soft gel-like ooze. It also constitutes a food supply for microbes, such as those that are part of our microbiome. In particular, mucus lines the respiratory, digestive and urogenital systems, but also structures in the visual and auditory systems, where it keeps pathogenic bacteria, virus and fungi away from epithelial cells they are only too keen to reach and infect. Our mucus – like those of many animals – does its job inside us.

However, in other animals, mucus is found on the external side of the skin where it forms a protective film that spans the whole body – think about frogs, worms, fish, slugs and snails.

We carry around rather a lot of mucus inside us. A 200 μm layer lines our intestine, forming about 2 m^2 of colonic slime... The slime is made up of various kinds of molecules like inorganic salts, antimicrobial enzymes, immunoglobulins and glycoproteins – and a whacking 94% of water. It is the water that gives mucus its gel-like nature: the oligosaccharide chains on glycoproteins sap up the water molecules, causing the mixture to expand and jellyfy, much like a dry sponge does when dipped into water. In the respiratory tract, foreign material is rapidly drenched in mucus as it is driven by cilia into the pharynx, where a cough or a sneeze will do the rest. The various shades of yellow cum green we observe are the signature of pathogenic infection.

Where do the components that compose mucus come from? From goblet cells, so named for their goblet-like shape – large and round at their base, and long and narrow from the middle up – with an apical crown that is folded many times to multiply their surface. Goblet cells are an integral part of

mucus-lined epithelia where they are scattered among other epithelial cells. Their nucleus is forced into the basal end of the cell body. Their Golgi apparatus – where (to cut a long story short) proteins are packed away into vesicles ready for secretion – is pushed into the middle of the cell, while the apical end is crammed with secretory vesicles full of glycoprotein, or mucin, that release their contents into, say, the intestinal lumen. Bring in some water, mix everything and you have mucus – which is repaired and replaced on a continuous basis.

It is the sialic acid in mucus that creates the protective barrier between pathogens and epithelial cells. Sialic acids are negatively charged 9-carbon monosaccharides that are popped onto the carbohydrate chains of glycoproteins. The most common sialic acid is N-acetylneuraminic acid. Sialic acid can affect a cell's behaviour and is involved in many important biological processes such as cell recognition, cell adhesion, cell signal transduction, protein folding..., and of course pathogen infection and mucus integrity. To date, about 50 different sialic acids have been described, all of which are derived from a molecule of neuraminic acid and are expressed at different stages of an organism's development or in different tissues.

Sialyltransferases are transmembrane enzymes, located in the Golgi apparatus and are responsible for transferring sialic acid to glycoproteins. There are about 20 different kinds of sialyltransferases, which have been classified into types according to where exactly sialic acid is added to

glycoconjugates – and how. In particular, goblet cell sialyltransferases belong to a type known as alpha-N-acetylgalactosaminide alpha-2,6-sialyltransferase 1, or more simply ST6, which refers to the type of glycosidic bond involved. Like all sialyltransferases, the enzymes have an N-terminal cytoplasmic tail, a transmembrane domain and a large COOH-terminal catalytic domain that protrudes into the Golgi lumen. The catalytic domain has four conserved motifs which, collaboratively, bind sialic acid and then transfer it to glycoproteins. This process known as sialylation seems to take place when goblet cells sense the presence of microbial pathogens in the mucus.

Consequently, not only is sialylation important in discouraging mucous pathogens but it is, inevitably, involved in mucus homeostasis and hence human health, not to mention the well-being of our microbiome. The intestinal lumen, mucus and commensalism are all part of one system, whose parts are intricately intertwined and depend on one another. A deficiency in sialylation creates an imbalance in mucus homeostasis and is thought to bring about diseases such as inflammatory bowel disease (IBD) which inflicts an estimated 10 million people worldwide. As sialyltransferases are involved in vital processes such as cell recognition and cell adhesion, problems with sialylation could also play a part in tumour cell migration, i.e. metastases. In both cases, treatments that specifically affect sialyltransferase function could therefore be of interest. Certainly, in retrospect, it is with far greater respect that I remember the drop on the end of Lady Clarke's nose.

Cross-references to UniProt

alpha-N-acetylgalactosaminide alpha-2,6-sialyltransferase 1, *Homo sapiens* (Human) : Q9NSC7

References

1. Yao Y., Kim G., Shafer S., *et al.*
Mucus sialylation determines intestinal host-commensal homeostasis
Cell 185:1172-1188(2022)
PMID: 35303419
2. Li Y., Chen X.
Sialic acid metabolism and sialyltransferases: natural functions and applications
Applied Microbiology & Biotechnology 94:887-905(2012)
PMID: 22526796